The Immune System as a Complex System

Eric Leadbetter
elead1@umbc.edu
CMSC 491H
Dr. Marie desJardins

Introduction

The immune system is one of the most critical support systems in a living organism. The immune system serves to protect the body from harmful external agents. In order to accomplish its goal, the immune system requires both a detection mechanism that will discern harmful agents (pathogens) from self and neutral agents and an elimination mechanism to deal with discovered pathogens. Different levels of organismic complexity have increasingly complex detection and elimination mechanisms.

The human immune system has a particular attribute that lends itself well to the study of complex systems: that of adaptation. The human immune system is able to "remember" which malicious agents have been encountered and subsequently respond more quickly when these agents are encountered again. In this way, the body can defend against infection much more efficiently. The problem with acquired immunity is that infectious agents are constantly evolving; thus, the immunological memory will lack a record for any newly evolved strains of disease.

In addition to acquired immunity, humans have an innate immunity, which is the form of immune system that is also present in lower levels of organismic complexity such as simple eukaryotes, plants, and insects. The innate immune system serves as a primary response to infection by responding to pathogens in a non-specific manner. It promotes a rapid influx of healing agents to infected or injured tissues and serves to activate the adaptive immune system, among other things.

A complex adaptive system is defined as such by the fact that the behavior of its agents change with experience as opposed to following the same rules *ad infinitum*. I will draw parallels between the immune system and complex adaptive systems that will illustrate how the immune system is an example of a biological complex adaptive system.

I will conclude with a discussion of my model of the adaptive immune system, written in NetLogo. Metrics of the system will be discussed as well as a reflection on how accurately (or inaccurately) the model represents its intended subject. Furthermore, a discussion of the techniques used to model the immune system will be presented.

The Immune System

As mentioned, the immune system is one of the most important systems in the body for survival. The immune system serves as a preventative and defensive mechanism against injury and infection for the body. It provides these services through a coordinated effort of many individual agents that all serve a specialized purpose. Beyond simply eliminating harmful agents, the immune system is able to distinguish between harmful and benign foreign agents.

The Leukocytes and their Functions

The functionality of the immune system is dependent on its components. Cytokines are an integral part of the immune system. Furthermore, the different aspects of the immune system have their own elements that serve special purposes. For example, the innate immune system involves elements such as phagocytes, neutrophils, and natural killer cells. The primary agents of the adaptive immune system are a type of leukocyte called lymphocytes, which are further divided into T cells and B cells[4]. Additionally, dendritic cells function as a link between the innate immune system and the adaptive immune system[1, 12].

Cytokines are protein structures that serve as a communication medium between cells. They are classified based on their structure and their intended receiver(s). Cytokines function by binding to particular surface receptors on their target cells. This leads to the alteration of cellular function[6]. Cytokines are used to trigger the production of T cells and also to attract other cells to the site of injury

to repair damage and defend against possible infection[24].

Phagocytes serve to dispose of pathogens and dead tissue. After activation, phagocytes engulf the target object and internalize it, where it is incorporated into the lysosome of the phagocyte. There, the target object is disposed of via destruction or attrition (starvation)[20]. A sub-type of phagocytes is the macrophage. Macrophages are essentially phagocytes that can move around by a process known as chemotaxis. However, they typically stay in a particular region and recruit more macrophages as necessary to deal with a problem[14]. Macrophages also play a significant role in the adaptive immune system, which will be covered shortly.

Two other types of cells of importance in the innate immune system are neutrophils and Natural Killer cells. Both serve as direct combatants against infection. Neutrophils serve by migrating toward infection sites via chemotaxis and recruiting other immune cells, in addition to direct combat[19]. Natural Killer cells primarily deal with tumors and virally infected cells; NK cells can either trigger apoptosis—programmed cell death—in infected cells or cause lysis—a degradation of the cell—in tumors. This difference in method is for containing viruses: apoptosis will kill the infecting virus inside the cell, whereas lysis would rupture the cellular membrane, releasing the virus to infection other cells[18].

In order for activation of the adaptive immune system to take place, a notice of infection must be communicated to the lymphocytes of the adaptive immune system. Dendritic cells serve this purpose. Dendritic cells, while similar in appearance, are unrelated to neurons. Dendritic cells reside on tissue that is exposed to the external environment (i.e., the skin or the stomach lining). They serve to present antigens to T cells in order to stimulate specific responses to pathogens[8]. Antigens are molecules that trigger the production of an antibody (in B cells) or the recruitment of combatant cells (by T cells) to counter whichever pathogen produces the antigen.

There exists a category of cells that specialize in efficiently presenting antigens to T cells. The antigen presentation is done via molecules called the major histocompatibility complexes (MHC). Every cell in the body has Class I MHC molecules; however, only professional antigen-presenting cells (APCs) use Class II MHC molecules to present their information[15]. Dendritic cells are one form of APCs. Other APCs include macrophages and B cells[2]. Macrophages, as mentioned before, are a major factor in the innate immune system. However, they also serve the purpose of presenting antigens. After phagocytosis, macrophages will present the antigen of the digested pathogen for detection by a T cell. B cells are able to perform a similar task, although they also serve entirely different purposes that will be covered shortly.

The adaptive immune system involves yet more types of cells. The cells involved in the adaptive immune system are called lymphocytes (or white blood cells). There are three types of lymphocytes, which are Natural Killer cells which have been discussed because they are involved in the innate immune system, T cells which drive the cell-mediated immune response (a subtype of the adaptive immune system), and B cells which are involved in both activation of the cell-mediated response and in a separate response type known as humoral immunity[13]. Additionally, macrophages play a role in the adaptive immune system.

First, I will discuss T cells, the major player in cell-mediated immunity. Cell-mediated immunity involves immune cells triggering apoptosis (programmed cell death) in infected cells and performing phagocytosis via macrophages, which activated T cells can stimulate into a more aggressive state[5]. There are several different types of T cells, all with specific purposes:

The first of these to mention are helper T cells (T_h cells). Unusually when compared to other lymphocytes, T_h cells are unable to kill pathogens; their purpose is to release cytokines after binding to their specific matching antigen (called their cognate antigen). Antigens must be presented to T_h cells by

APCs. These cytokines are used to activate and stimulate growth of cytotoxic T cells (to be discussed), activate the adaptive response of macrophages, and to help with the maturation of B cells. T_h cells, like several other leukocytes, go through a maturation process which will be discussed in a subsequent section.

Secondly, there are cytotoxic T cells (T_c cells). T_c cells induce death of cells infected by pathogens. Their activation is triggered by binding to antigens presented at Class I MHC molecules on *any* cell, as opposed to the activation of T_h cells by Class II MHC molecules on macrophages, dendritic cells, and B cells[7].

Thirdly, memory T cells can be thought of as the "veterans" of the cell-mediated immune response. Memory T cells are T cells that have been previously activated by their cognate antigen. This is significant because if a memory T cell is activated by its cognate again, it is able to rapidly reproduce to more efficiently defend against an infectious agent[16].

Alternatively to T cells, B cells form an entirely separate type of adaptive immune response called the humoral immune response. The primary function of B cells is to produce antibodies, which are the central effectors of the humoral immune system. Antibodies function by binding to antigens which effectively "tags" the pathogen or infected cell for attack by other immune cells; additionally, the binding of antibodies to antigens can sometimes block parts of a pathogen that are required for its effectiveness, essentially neutralizing it. There are two main types of B cells. The first are plasma cells; plasma cells are B cells that have been exposed to their specific antigen and rapidly produce antibodies to bind to the antigen. Once their specific pathogen has been dealt with, plasma cells undergo apoptosis. The second type of B cell is the memory B cell which is analogous to the memory T cell[3].

We will revisit the development of the components of the adaptive immune system in the later section that defines how the immune system is a complex system.

Complex Adaptive Systems

Definitions

A complex system is a collection of agents that interact with one another and their environment according to some rule set to produce some form of emergent behavior. Emergent behavior refers to behavior that is not apparent by looking exclusively at the individual agents. Three major concepts that may (individually or combined) indicate a complex system are those of parallelism, self-reference (i.e., recursion), and adaptation.

Briefly, the idea of parallelism refers to the concept that many agents within the system perform the same task simultaneously. Self-reference, or recursion, refers to the concept that similar emergent behavior can be observed at subsequently lower levels of a system. Examples of these two ideas are the schooling of fish for parallelism and the calculation of factorials in mathematics for recursion (each factorial is calculated using factorials of lesser numbers).

Adaptation, the form of complexity most important to this paper, is essentially learning. The agents within a system are able to detect what occurs in their environment and respond to it by changing their behavior. Adaptation can be on a singular scale (i.e., each agent changes individually in response to some encounter(s)) or it can be on a population scale. That is, over time the general characteristics (behaviors and traits) of a population will change in response to the environment.

The greatest example of adaptation is evolution by natural selection. Individually, organisms of a species will adapt to day-to-day environmental changes such as weather. However, when viewed as agents, the genes that produce the fittest—that is, most likely to reproduce—individuals will be selected for. As a result, the entire *population*, as opposed to a particular individual, will adapt itself to be best able to survive in its environment.

Perhaps obviously, a complex adaptive system is a complex system that is defined prominently by adaptive behavior. As stated by Holland, complex adaptive systems (cas) have "four major features": parallelism as defined earlier; "conditional action," which means that actions of agents are defined by feedback that they receive from themselves or the environment; "modularity," which is defined by subgroups of rules that form particular behaviors (these subgroups—called "subroutines"—can, "be combined to handle novel situations"); and finally adaptation as defined above[11].

Components and Classifier Systems

Holland defined a type of system that describes the agents in a complex adaptive system and how they learn and adapt to their environment. This system is known as a classifier system (abbreviated, by Holland, to 'cfs').

Cfs are made up of five components: a list of classifiers, a list of signals, detectors, effectors, and reservoirs[11].

The list of classifiers contains the rules of a particular agent, defined in three parts. The first two parts are of an if-then structure. The first part is a particular condition that the agent can be in. The condition can be matched by a signal from the environment and is defined as a *k*-length binary string that may have wildcards (#) that match either 1 or 0 in some locations. The second is the signal that the classifier will trigger, if selected. The third part is the strength of the particular classifier; this strength is a measure of the classifier's previous contributions to the receipt of a reward.

The list of signals comprises all of the signals that correspond to the classifiers that are appropriate to the current state of the environment. That is, classifiers that most closely match the current state of the environment are selected, and their respective signals comprise the signal list.

The detectors report environmental information back to the classifiers; the classifiers that most accurately match the signals reported by the detectors are selected to compete for effection (i.e., the classifier's signal will be applied by the effectors).

Effectors apply the signals of the winning classifiers to the environment.

Reservoirs provide a measure of the system's ability to ensure its survival. That is, they constantly deplete and particular effector actions can increase them. How frequently the reservoirs are refilled indicates how efficient the classifiers of the system are[11].

The learning process of cfs can be explained as follows. Detectors place signals on the signal list that represent environmental information. As mentioned before, classifiers that match the signals on the list are selected. Matching classifiers compete with each other based on their strength; the classifiers with the greatest fitness are then selected to be effected on the environment. At this point, the first part of the learning system is encountered; selected classifiers give some of their strength (called bids) to the classifiers that led to their being selected. In this way, chains of classifiers (rules) are developed. The signals from selected classifiers are placed on the message list; at this point, the effectors apply the signals to the environment. Some of the signals will receive feedback from the environment (payoff); this payoff will strengthen (or weaken) the classifier of that signal, thus causing it to be chosen more (or less) readily over other classifiers. In this way, the classifier system can learn which rules are better and which are worse[9].

Classifiers that have been shown to be useless or harmful will be weeded out and replaced with new classifiers. The most effective way of doing this is via a genetic algorithm, essentially "breeding" effective classifiers together to combine traits of each successful classifier potentially making an even more successful classifier[11].

The Immune System as Complex System

In order to establish the immune system as an example of a complex adaptive system, I explore the way in which the adaptive immune system develops, then follow with more detailed descriptions of how it functions.

Development of the Immune System

We will begin with a description of the development process for T cells. T cell development primarily takes place in the thymus; while in the thymus, each T cell undergoes two forms of selection, called positive and negative selection. Positive selection ensures that only T cells with some form of detection of "self" antigens will persist; all other cells undergo apoptosis (see "Leukocytes and their Functions" above). "Self" antigens are antigens that are produced by components of the host. T cells must be able to recognize self antigens in order to discern self from non-self. T cells that survive positive selection then undergo negative selection. During negative selection, any T cells that bind too strongly to self antigens are eliminated, thus decreasing the possibility of autoimmune disease (i.e. the immune system attacking the host body). After negative selection is complete, only T cells that recognize self but do not *target* self remain and exit the thymus as mature, naïve T cells[22].

A mature, naïve T cell waits in the body until it encounters a pathogen as yet unknown by the body whose antigen is its cognate. When this binding takes place, appropriate immune cells will be activated (i.e. T_c cells and macrophages) to combat the infection. Additionally, T_h cells will activate B cells to produce antibodies. After a T cell has been activated, it may become a memory T cell[17]. Memory T cells, as mentioned earlier, are able to rapidly reproduce upon encounter with their respective antigen, enabling a much faster immune response; memory cells represent the learning behavior of the immune system.

The development of B cells (which takes place exclusively in bone marrow) is similar to that of T cells. B cells undergo a negative selection process, ensuring that B cells do not respond too strongly to self antigens. After leaving the bone marrow, if B cells are activated (i.e., bind to an antigen) they will emit antibodies and reproduce, effectively cloning themselves. This enables more antibodies to be produced to counteract whatever antigen is present at the time[3]. Some of the new B cells will become memory B cells which serve an analogous purpose to memory T cells.

Parallels Between Immune System Development and CAS

There are clear parallels between the development of the adaptive immune system and classifier systems that are the trademark of complex adaptive systems. The T and B cells are produced with essentially random binding sites, similar to the initialization of the classifiers in a classifier system. Said T and B cells are tested against self antigens and those that respond too readily to self are eliminated from the pool; this is clearly the testing of classifiers against the environment, and the removal of weak or harmful classifiers. Ironically, unlike Holland's ideal classifier system that uses a genetic algorithm to generate new and potentially more useful classifiers, more random T/B cells are produced to take the place of those that were removed. Finally, once matured, the lymphocytes disperse through the body. There they are again tested against the environment. Those that are activated by antigens will generate memory cells. This is, in essence, receiving maximal payoff from the environment for a particular classifier and giving that classifier infinite strength, ensuring its persistence in the system. From then on, whenever an antigen that is recognized by a memory cell is present, the response by the immune system to that pathogen will be swift and deadly. This relates to a particular signal being presented to the classifier system and there being one definitive classifier that is selected and whose signal is effected. Finally, the continued survival of the host can be thought of as the refilling of the classifier system's reservoir. Clearly, the development and functionality of the adaptive immune system is an example of a

classifier system in action. Thus, it may actually be more accurate to say the entire human body is a complex adaptive system, with the immune system being one agent of it capable of responding to environmental changes regarding disease and infection.

Model Discussion

The model I have constructed is a simplified simulation of the adaptive aspect of the human immune system. The first version of the model lacked this adaptive nature; all lymphocytes were generated with pseudo-random type (analogous to an antigen) and all diseases were spawned with a random presenting antigen.

In the updated model, a disease spawned from an earlier generation disease (as opposed to one that randomly enters the system) will receive the same presenting antigen as its parent; diseases that randomly enter the system still receive random presenting antigens. This weakly indicates selection in diseases, because diseases that survive longer will be able to spawn more diseases of the same type.

The more significant update to the model is the introduction of adaptive behavior of the immune system. The immune system now remembers which diseases it has encountered and produces lymphocytes in proportion to the most abundant disease types. For example, if the system recognizes that Type 1 diseases are encountered 20% of the time, each time new lymphocytes are spawned 20% of the new lymphocytes will respond to Type 1 diseases.

This is accomplished by maintaining a table that stores a probability of appearance for each disease type. The values in this table are calculated as a rolling sum of the diseases of type *i*, divided by a rolling sum of the total number of diseases seen (**Equation 1**). Rolling sum means that at each time step, the difference between the current value and the previous value is added to the previous value, providing a value that takes into account newly introduced as well as removed diseases.

$$Prob_i = \frac{[count(disease_i) - prev(disease_i)] + prev(disease_i)}{[count(diseases) - prev(diseases)] + prev(diseases)}$$

Equation 1

The table effects only the types of lymphocytes spawned; it has no effect on the diseases produced.

Metrics

At this point, I will discuss measurements that have been taken from the model. As the number of diseases is static (user controlled), the only measurement of significant interest in the system is some measurement of "health". Health is defined as the percentage of red cells present in the system. It is calculated as the number of red cells present at the present time step divided by the number of patches in the world minus the (also healthy) lymphocytes (**Equation 2**). This serves to represent how healthy our model organism. The correctness of this measure can be seen by considering the complement: more diseases present in an organism indicate severity of sickness. Thus, we can extrapolate that more red

cells present indicates healthiness. Additionally, it serves as a measure of the effectiveness of the immune system; the presence of a greater number of red blood cells can be directly attributed to the ability of the immune system (lymphocytes) to combat diseases.

$$Health = \frac{count(red\ cells)}{count(patches) - count(lymphocytes)}$$

Equation 2

Results

The following images indicate the health over time with different levels of adaptive behavior present in the model. All graphs were constructed from runs of the model with user parameters the same. The model was run with maximum infectivity, i.e., diseases will definitely spawn when given the opportunity and the maximum number of disease types allowed is selected. Additionally, the model was run with maximum defense, i.e., lymphocytes spawn as rapidly as possible and each survives for the longest allowed time.

The first image shows the health of the model organism with no adaptive behavior (**Figure 1**). The next image indicates health when the immune system learns, but there is no generational continuity in the diseases (new diseases always spawn with random disease types) (**Figure 2**). Clearly there is a huge advantage for the immune system in this case. The next image shows generational continuity in diseases but no learning in the immune system (**Figure 3**). Strangely, this situation seems to be better for the immune system than all-random diseases. The final image indicates the situation where both forms (immunological and generational continuity) of adaptation are included (**Figure 4**).

Interestingly, it does not show a significant improvement over the random immune-adaptive disease situation. The maximum health appears the same in both cases and the general shape of the graph is similar. But we know that the adaptive immune system is better, based on the enormous difference in health between Figures 1 and 2. Thus, it is of note that there are more and deeper valleys in Figure 3 than in Figure 4, indicating that on average the adaptive immune system keeps the model organism healthier than a completely random one.

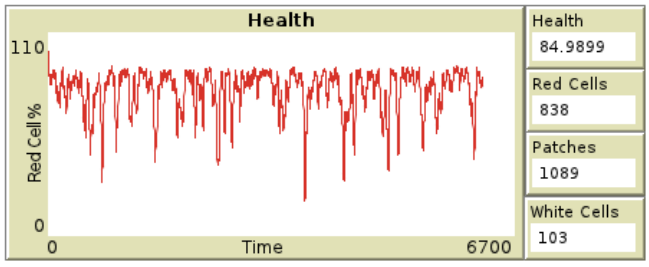

Figure 1

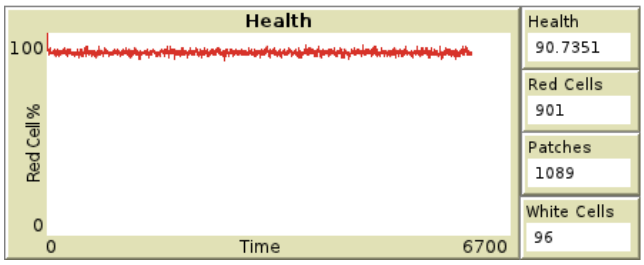

Figure 2

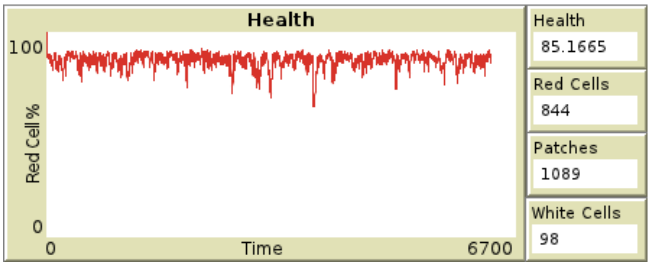

Figure 3

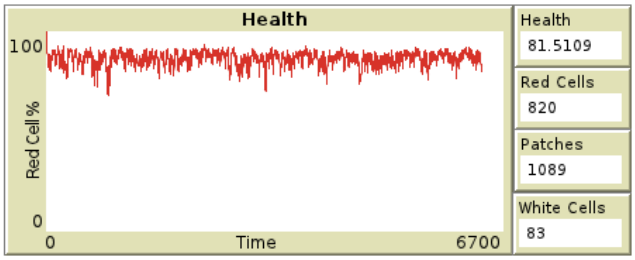

Figure 4

Accuracy

Obviously the accuracy of the model is limited. It abstracts away key components of the immune system such as the entire innate and humoral immune responses and does not follow the natural training process for response to infection (progression from marrow to thymus and positive and negative selection). Additionally, the lymphocytes represented are neither true T_h cells nor true macrophages, but a hybrid of the two: each lymphocyte has a type and moves towards and kills exclusively diseases of that type. In this way, they have the activating characteristic of T_h cells as well as the phagocytotic characteristic of macrophages.

However, the model is not completely inaccurate. Although the lymphocytes each have a type, it can be thought of that the T_h cells are hidden or represented globally and trigger the macrophages (lymphocyte agents) to move toward the specific diseases. The idea of "global" or "hidden" T_h cells is strengthened by the fact that the learning of the system is a global table that can be thought of as analogous to memory T cells. Furthermore, the fact that more lymphocytes responsive to a particular type are spawned when the probability of encountering that type is raised is analogous to memory T cells rapidly spawning T_h cells in response to activation.

Conclusion

Through the exploration of the many components of the immune system and the explanation of complex adaptive systems that I have presented, it is clear that the adaptive immune system is indeed a form of classifier system. The development pattern of the body's resistance to diseases follows the same environmental reinforcement strategy that is present in Holland's classifier systems, which serve to define the behavior agents in complex adaptive systems. I have shown that the immune system is capable of remembering what diseases it has encountered in the past, and changing its future behavior based on these memories. Finally, the agents in the immune system operate all perform their individual jobs at the same time as similarly functioning agents, presenting parallel behavior that is frequently an indicator of a complex system. Because the immune system acts as one agent (a classifier system), it is more accurate to describe the human body as a complex adaptive system which adapts to its environment—with the immune system handling diseases—rather than the immune system itself being a complex adaptive system.

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